

## Short reports

# Waterhouse–Friderichsen syndrome complicating primary biliary sepsis due to *Pasteurella multocida* in a patient with cirrhosis

M Ip, J G C Teo, A F B Cheng

### Abstract

*Pasteurella multocida* is an opportunistic pathogen causing bacteraemia in patients with liver dysfunction. A fulminant case of acute cholecystitis and septicaemia caused by *P. multocida*, complicated by Waterhouse–Friderichsen syndrome without skin haemorrhage, is reported in a previously healthy 64 year old Chinese woman. The patient presented with a six hour history of sudden onset epigastric pain, vomiting, chills, and rigors. A presumptive diagnosis of cholangitis with septic shock was made. Disease progression was rapid and the patient died within eight hours of symptom onset. This case is further proof that skin and mucosal haemorrhages are not an essential feature of Waterhouse–Friderichsen syndrome and this condition should be suspected in all patients presenting with sudden illness and fulminant septicaemia.

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Keywords: Waterhouse–Friderichsen syndrome, cirrhosis, *Pasteurella multocida*.

*Pasteurella multocida*, a small Gram negative coccobacillus, causes a variety of infections in humans. The organism is distributed worldwide, occurring as a commensal in the nasopharynx and gastrointestinal tract of many domestic and wild animals. The type of infection seen most frequently in humans is cellulitis following an animal bite.<sup>1</sup> However, infections may also occur without exposure to animals. It has rarely been reported as a cause of intra-abdominal infection and septicaemia in patients with cirrhosis.<sup>2,3</sup> A case of Waterhouse–Friderichsen syndrome, without skin haemorrhage, complicating acute cholecystitis and bacteraemia caused by *Pasteurella multocida* in a patient with hepatitis B associated cirrhosis is reported.

### Case report

A previously healthy 64 year old Chinese woman was admitted with a six hour history of sudden onset epigastric pain, vomiting, chills, and rigors. There was no history of recent exposure to animals or invasive medical

procedures. On admission, she was jaundiced, febrile (39.5°C) and hypotensive (systolic pressure 70 mmHg and central venous pressure 5 cm H<sub>2</sub>O). The patient was tender in the right upper abdominal quadrant. A presumptive clinical diagnosis of acute cholangitis with septic shock was made. Empirical intravenous antibiotic therapy with ampicillin, cefuroxime and metronidazole was initiated. The patient was resuscitated with intravenous fluids and her blood pressure stabilised.

Laboratory investigations revealed the following: haemoglobin, 12.7 g/dl; white cell count,  $9.2 \times 10^9/l$ ; platelet count,  $11 \times 10^9/l$ ; normal electrolyte and amylase values; bilirubin, 33 µmol/l; alanine aminotransferase, 143 U/l; alkaline phosphatase, 92 U/l; albumin, 15 g/l; total protein 58 g/l; prothrombin time, 26.4 seconds; and activated partial thromboplastin time, 88.6 seconds. These findings confirmed disseminated intravascular coagulopathy and impaired liver function.

Emergency endoscopic retrograde cholangiography was planned, but abandoned when the patient sustained a cardiac arrest on arrival at the Radiology Department. She was then transferred to the Intensive Care Unit for further management. The patient sustained a second cardiac arrest and died one and a half hours after admission to hospital. Permission to perform a necropsy was granted.

### Pathology

At necropsy, there were no wounds or localised skin infections, and no skin or mucosal haemorrhages.

Internal examination revealed the classic appearances of Waterhouse–Friderichsen syndrome with massive bilateral adrenal haemorrhages. Microscopic examination revealed haemorrhage within the adrenal cortex and medulla, extending into the perirenal fat. Multiple visceral petechiae were also found.

Other significant findings were mainly within the hepatobiliary system. The gall bladder was oedematous and haemorrhagic, and contained multiple small calcium bilirubinate stones. The rest of the extrahepatic biliary tree was unremarkable. The liver showed micronodular cirrhosis with severe congestion and haem-

Department of Microbiology,  
The Chinese University of  
Hong Kong, Prince of Wales  
Hospital, Shatin, Hong Kong  
M Ip  
A F B Cheng

Department of Anatomical and  
Cellular Pathology  
J G C Teo

Correspondence to:  
Dr M Ip.

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orrhage. There was also evidence of portal hypertension, with ascites (350 ml) and congestive splenomegaly (399 g). There were no oesophageal varices. Histologically, the liver showed sinusoidal congestion and extensive haemorrhage into the fibrous septae separating regenerative nodules. Hepatocytes were positive for hepatitis B surface and core antigens on immunohistochemistry.

### Microbiology

*P. multocida* was isolated from an antemortem blood culture (taken on admission), from a postmortem blood culture and, in pure culture, from bile aspirated from the gall bladder at necropsy. The isolates were non-motile, Gram negative coccobacilli yielding mucoid, grey, convex non-haemolytic colonies on horse-blood agar at 37°C after overnight incubation. The organisms did not grow on MacConkey agar. They produced acid from glucose and sucrose but not from lactose. They were oxidase and catalase positive, and the API20E system (BioMerieux SA, Marcy l'Etoile, France) identified the three isolates as *P. multocida* (reaction code, 0044504). The antibiotic sensitivity patterns of the three isolates were identical on testing with Stoke's agar disc diffusion method using Mastring-S (Mast Diagnostics, Liverpool, UK) and were sensitive to penicillin, ampicillin, cephalosporins, aminoglycosides, and quinolones.

### Discussion

This is the first documented case of Waterhouse-Friderichsen syndrome complicating *P. multocida* septicaemia. The classic features of Waterhouse-Friderichsen syndrome are sudden onset of illness with rapid progression, manifestation of systemic haemorrhagic, especially in the skin, mucous membranes and serosal surfaces, shock and death within 24 hours, and haemorrhage into both adrenals on post-mortem examination. In this instance the absence of skin or mucosal haemorrhages may have confounded the diagnosis. This is the third recorded case of Waterhouse-Friderichsen syndrome without skin haemorrhage, the two previous cases occurring in young children with *Haemophilus influenzae* bacteraemia.<sup>4</sup>

Waterhouse-Friderichsen syndrome is rarely seen in adults and is usually related to disseminated intravascular coagulation in those with bacteraemia. Haemorrhagic destruction of the adrenals leads to primary acute adrenocortical insufficiency and circulatory collapse. Common causative organisms include *Neisseria meningitidis* and *H. influenzae*. Isolated cases of Waterhouse-Friderichsen syndrome have also been reported in association with *Capnocytophaga* species, DF-2,<sup>5</sup> *Escherichia coli*<sup>6</sup> and *Acinetobacter calcoaceticus*<sup>7</sup> bacteraemia. Like *P. multocida*, DF-2 is a Gram negative bacillus occurring as an oral commensal of animals and is an opportunistic pathogen in humans. It is also usually transmitted through animal contact or bites, and typically causes meningitis and septicaemia in immunocompromised patients.

In immunocompromised patients *P. multocida* may cause severe localised infections such as meningitis, pneumonia and intra-abdominal infections.<sup>3</sup> Reported intra-abdominal infections have included primary bacterial peritonitis in patients with cirrhosis, a few of whom underwent endoscopy,<sup>8,9</sup> peritonitis due to a ruptured viscus, intra-abdominal abscesses, and postoperative wound infections.<sup>8</sup> To our knowledge, this is the first documented case of *P. multocida* causing primary biliary sepsis. Our patient had acute cholecystitis and bacteraemia with *P. multocida* isolated from the bile and blood. The causative organisms of these conditions, however, are usually enteric bacilli or streptococci.

Bacteraemia due to *P. multocida* is relatively infrequent but may also occur in immunocompromised patients, particularly in those with liver dysfunction. Localised sites of infection were present in over half of these reported cases. Raffi *et al.*<sup>3</sup> stressed the prognostic importance of the underlying disease, cirrhosis and malignancy being associated with a poorer outcome. In their series these authors reported a mortality rate of 31% in patients with *P. multocida* bacteraemia, with all fatalities occurring in patients with severe decompensated cirrhosis. Our patient had previously undiagnosed, but histologically confirmed, hepatitis B associated cirrhosis with biochemical evidence of impaired liver function.

There was no documented history of recent exposure to animals or invasive medical procedures in the case reported here. Exposure to animals was absent in 21% of the cases of *P. multocida* bacteraemia reported in the literature.<sup>3</sup> Another possibility is that previous colonisation of the upper respiratory and gastrointestinal tract may become apparent in immunocompromised patients or following procedures such as endoscopy.

This case illustrates that *P. multocida* can cause severe infection in immunocompromised patients, particularly in those with cirrhosis. Therefore, *P. multocida* should be considered as a possible cause of bacteraemia in such patients, even if a history of exposure to animals is absent. Skin or mucosal haemorrhages are not an essential feature of Waterhouse-Friderichsen syndrome. Development of this catastrophic complication should be suspected in all cases presenting with sudden illness and fulminant septicaemia. Confirmation of adrenal pathology by abdominal ultrasonography<sup>10</sup> may permit early diagnosis and prompt treatment with glucocorticoid replacement therapy. In our patient, however, the rapid progression of her illness (with death occurring within eight hours of onset of symptoms) was such that the outcome probably could not have been altered, even if Waterhouse-Friderichsen syndrome had been diagnosed pre-mortem.

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## Microbiological investigation of polyarthralgia

J Wynne Jones, J V S Pether, R W P Frost

### Abstract

**Results of serological investigations on patients with joint pain, arthralgia or polyarthritis were analysed and this information was used to develop a diagnostic algorithm to ensure optimal utilisation of laboratory resources. Accordingly, all cases are now examined for parvovirus IgM, mycoplasma IgM and streptococcal antibodies. Further tests are undertaken by following the algorithm after obtaining supplementary information from a questionnaire. This approach is put forward as a preliminary standard which other laboratories may like to evaluate and develop according to local requirements.**

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**Keywords:** Polyarthralgia, algorithm.

Selection of the appropriate serological investigations in patients with arthralgia often poses difficulty.<sup>1,2</sup> To ensure the optimal use of resources and time, it is important that the relevant investigations are chosen from the wide range of available tests.

### Methods

To determine the current practice in our laboratory, the results of the serology performed over the last six months on patients with a clinical history of joint pain were analysed. On the basis of these observations, guidelines for the future investigation of patients with polyarthralgia were prepared.

### Results

The serological findings for the 140 patients studied are shown in the table. An outbreak of parvovirus infection coincided with this study and polyarthritis was attributed to this infection in one quarter of all patients investigated.

Four serum samples had antistreptolysin O (ASO) titres >800 units/ml and DNase antibodies above 300 units/ml. Six serum samples had ASO titres between 500 and 800 units/ml, all indicative of recent streptococcal infection. An additional two serum samples had raised anti-DNase antibodies with a normal ASO which, in the presence of a compatible clinical history, were also considered suggestive of a streptococcal illness. In total, 12 serum samples exhibited evidence of recent streptococcal infection—that is, 8.6% of all the patients studied.

The heterophil antibodies detected by the positive monolateral tests were not confirmed as recent Epstein-Barr virus (EBV) infections—that is, exhibiting a positive immunofluorescence test for EBV capsid antibody in the presence of a negative enzyme linked immunosorbent assay (ELISA) test for EB nuclear antigen antibody. In eight patients the positive monolateral test appeared to be related to the presence of recent infection with parvovirus, a difficulty that has been reported previously.<sup>3</sup>

**Public Health Laboratory,  
Musgrove Park Hospital,  
Taunton,  
Somerset, TA1 5DB**  
J Wynne Jones  
J V S Pether  
R W P Frost

Correspondence to:  
Dr J Wynne Jones.

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### Tests performed on 140 serum samples submitted for investigation of polyarthralgia

Investigation	Number of samples tested	Number of samples positive (%)
Routine virus screen	117	0
ASO	117	12 (10.3)
Monolateral (heterophil antibodies)	108	10 (9.2)
Rubella IgM (ELISA)	110	1
Mycoplasma IgM (ELISA)	101	2 (1.9)
Parvovirus IgM (radioimmunoassay)	122	35 (28.7)
Lyme serology (ELISA)	18	1

Routine viral CFTs include the following antigens: influenza A and B; adenovirus; respiratory syncytial virus; Q fever; and Psittacosis. Serology tests for *Leptospira* (n=3), *Brucella* (n=2), *Yersinia* (n=2), *Toxoplasma* (n=3), hepatitis B (n=1), and *Chlamydia* (n=2) were also performed with negative results.